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Luteinizing Hormone-Releasing Hormone (LHRH)-Independent Precocious Puberty Unresponsive to LHRH Agonist Therapy in Two Girls Lacking Features of the McCune-Albright Syndrome

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ABSTRACT. Two girls with precocious puberty (chronological age, 1 and 4 yr; bone age, 3 and 6 yr, respectively) were initially given the diagnosis of idiopathic, central precocious puberty and treated with the LHRH agonist deslorelin (D-Trp^6-Pro^9-NEt-LHRH) for 5 yr. Unlike other girls with central precocious puberty, both had persistently elevated rates of growth and bone maturation, and both menstruated during therapy. One girl had episodic ovarian enlargement and markedly elevated serum estradiol levels due to recurrent unilateral ovarian cysts. Although the bone and skin manifestations of McCune-Albright syndrome were absent, we hypothesize that the underlying defect of McCune-Albright syndrome was expressed in the ovaries, but not in the skin or bones, of these two girls. One of these girls appeared to benefit from the aromatase inhibitor testolactone, which is effective in suppressing precocious puberty in girls with the McCune-Albright syndrome. (*J Clin Endocrinol Metab* **73:** 1370–1373, 1991)

CLINICAL trials have shown the effectiveness of the agonist analogs of LHRH in treating children with LHRH-dependent precocious puberty (1, 2). In contrast, children with LHRH-independent precocious puberty, such as girls with the McCune-Albright syndrome (MAS) and boys with familial male precocious puberty, do not benefit from LHRH analog treatment unless LHRH-dependent puberty has occurred secondarily (3–6).

Here, we report our observations in two girls with precocious puberty who failed to respond clinically to LHRH analog therapy despite suppression of serum gonadotropin levels and who lacked the skin and bone lesions characteristic of MAS. We suggest that autonomous ovarian hyperfunction, similar to that observed in MAS, may account for the signs of puberty in these two patients.

Subjects and Methods

Patient 1 had vaginal bleeding and breast development at 6 months of age. At the age of 1 1/12 yr, she had increased stature, bone age (7), and growth rate (8) (Table 1). Ovarian volumes (9), serum estradiol (E_2) (6), and LH and FSH responses to LHRH (10) were normal for a prepubertal girl (Table 2). Her breasts and pubic hair were pubertal stage II (8).

Patient 2 had vaginal bleeding and breast development at the age of 3 yr. At 4 4/12 yr, she had an advanced bone age and rate of growth (Table 1). The right ovary was enlarged, and both ovaries had small (<1 mL) cysts. Serum E_2 and the LH and FSH responses to LHRH were in the normal prepubertal range (Table 2). Her breasts were stage III, and pubic hair was stage II.

No café-au-lait pigmentation was found in either girl, and bone scans showed no evidence of polyostotic fibrous dysplasia. Computed tomography of the sella and hypothalamus was unremarkable. Thyroid and adrenal function were normal initially and at all subsequent evaluations.

A presumptive diagnosis of idiopathic central precocious puberty was made, and the patients were treated with the long-acting LHRH agonist deslorelin (D-Trp^6-Pro^9-NEt-LHRH; 4 μg/kg·day, sc) at 2000 h. Patient 1 was treated with LHRH agonist for 5 yr; therapy was then changed to the aromatase inhibitor testolactone (40 mg/kg·day, orally), which has been effective in treating girls with puberty due to MAS. Patient 2 was treated with LHRH agonist for 5.7 yr, after which treatment was stopped.

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TABLE 1. Age, bone age (BA), rate of change of bone age *vs.* chronologic age (ΔBA/ΔCA), growth rate, growth rate SD, height, height SD, and predicted adult height in two patients during and after 5 yr of LHRH analog therapy

	Start of therapy	Yr of LHRH agonist therapy					Yr after therapy[a]	
		1	2	3	4	5	1	2
Patient 1								
Age (yr)	1.1	2.1	3.0	4.0	4.9	5.8	7.0	8.2
BA (yr)	3.0	4.5	6.0	7.8	9.0	10.5	11	11
ΔBA/ΔCA	2.7	1.5	1.7	1.8	1.3	1.8	0.4	0
Growth rate								
cm/yr	16.8	9.2	9.9	9.5	12.2	6.9	6.7	6.2
SD	+1.3	+1.1	+1.3	+1.9	+5.3	+0.6	+0.9	+0.5
Ht								
cm	81	97	107	116	128	134	142	149
SD	+1.9	+3.2	+3.2	+3.3	+4.2	+3.9	+3.9	+3.8
Predicted ht				148	155	152	157	165
Patient 2								
Age (yr)	4.3	5.3	6.8	8.0	9.0	10.0	11.6	12.7
BA (yr)	5.8	7.8	9.5	10.8	12.0	12.5	15.0	15.0
ΔBA/ΔCA	1.5	1.8	1.1	1.1	1.2	0.5	1.3	0
Growth rate								
cm/yr	9.4	10.7	7.5	7.0	6.0	4.0	3.0	1.4
SD	+2.0	+4.2	+1.8	+1.4	+0.4	−2.3	−4.5	−3.6
Ht								
cm	104	116	126	133	139	143	149	150
SD	+0.9	+1.5	+1.5	+1.4	+1.6	+1.6	−0.3	−0.4
Predicted ht (cm)		148	149	148	150	152	150	152

[a] Patient 1 was treated with testolactone after LHRH agonist therapy was discontinued.

TABLE 2. Mean ovarian volume (MOV), serum estradiol (E_2), and peak response of LH and FSH after 100 μg LHRH, iv, in two patients during and after 5 yr of LHRH agonist therapy

	Start of therapy	Yr of LHRH agonist therapy					Yr after therapy	
		1	2	3	4	5	1	2
Patient 1								
MOV (mL)	0.4	0.7	0.7	0.5	2.3[a]	1.0	3.6	5.8
E_2 (pmol/L)	77		26	70	92	73	40	95
LH (IU/L)	7.2	2.6	2.0	2.1	2.7	0.8	2.3	9.9
FSH (IU/L)	52.5	1.2	2.7	1.2	1.1	0.5	3.2	13.6
Patient 2								
MOV (mL)	1.4[a]	18.1[b]	5.2[c]	7.3	3.3	6.9[d]	14.0[e]	5.0
E_2 (pmol/L)	161	1681	617	95	128	103	73	207
LH (IU/L)	7.7	2.8	2.6	3.2	3.5	3.7	9.2	14.2
FSH (IU/L)	43	0.2	2.1	2.8	1.3	1.0	1.5	14.6

Normal values for prepubertal girls: MOV, <1 mL (11); E_2, <70 pmol/L (6); peak levels after LHRH: LH, 10.6 ± 3.5; FSH, 23.3 ± 12.1 (12).
[a] Small (<1 cm) cysts in both ovaries.
[b] Left ovarian cyst, 4.0 cm in greatest dimension.
[c] Left ovarian cyst, 1.5 cm in greatest dimension.
[d] Left ovarian cyst, 3.5 cm in greatest dimension.
[e] Left ovarian cyst, 2.5 cm in greatest dimension.

Evaluations were performed every 6–12 months. Mean ovarian volume was calculated as the mean of right and left ovarian volumes, using pelvic ultrasonography. Serum LH and FSH were measured after a 100-μg injection of LHRH, and serum E_2 was measured at 1000, 1400, 2200, and 0200 h, using modifications of previously reported methods (11–13). Adult stature was estimated by the Bayley-Pinneau method (7).

The study protocol was approved by a Clinical Research Committee, and informed consent was obtained from a parent.

Results

Patient 1

Linear growth rate SD score (SD) and rate of bone age maturation (ΔBA/ΔCA) remained elevated during the first 4 yr of LHRH agonist therapy (Table 1), and there were four episodes of menstrual bleeding (Fig. 1). Although her ovarian volume and E_2 level remained close

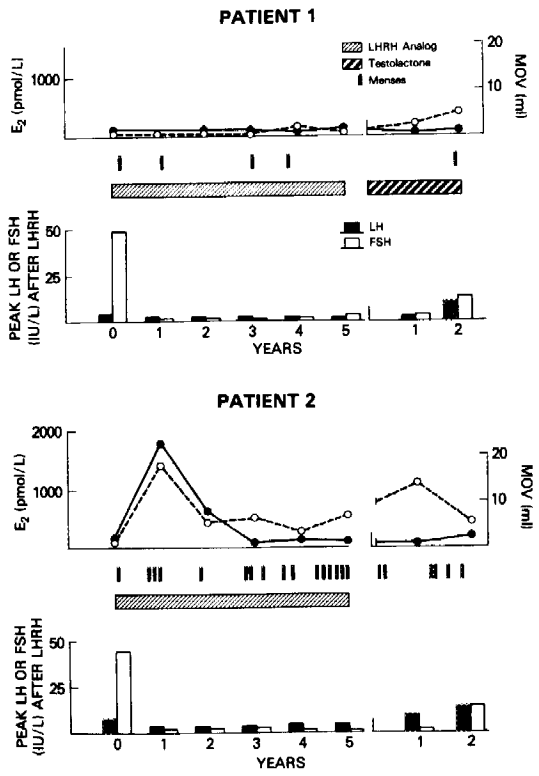

FIG. 1. Serum E_2 (●), mean ovarian volume (MOV; ○), peak LH (■), and FSH (□) after LHRH treatment and episodes of menses (*vertical bars*) in two girls with gonadotropin-independent precocious puberty during therapy with LHRH analog (*lightly hatched bar*) and testolactone (patient 1; *heavily hatched bar*).

to normal, prepubertal levels for the initial 3 yr of treatment, her growth rate, and serum E_2 increased during the fourth year, and bilateral ovarian cysts were seen. Serum gonadotropin levels remained suppressed throughout treatment (Table 2), which appeared to confirm the parents' assertion of full compliance with the treatment regimen. Breast development remained at stage III during therapy; pubic hair progressed to stage IV by the fifth year. Between 3–5 yr of therapy, the predicted adult stature rose from 148 to 152 cm.

The evidence of nonresponsiveness to LHRH agonist led us to revise the diagnosis to LHRH-independent precocious puberty and to discontinue LHRH agonist. During 2 yr of treatment with testolactone, her bone age did not advance. At the start of the second year of treatment, there was a single episode of vaginal bleeding and an increase in ovarian volume, while the LH and FSH responses to LHRH retained a normal prepubertal pattern. Her predicted adult stature increased to 165 cm.

Patient 2

The growth rate and growth rate SD remained elevated during the first 3 yr of LHRH agonist treatment (Table 1). She had frequent menses during therapy (Fig. 1), her ovarian volume was often increased due to cysts in the left ovary, and her serum E_2 levels were elevated. Despite these persistent signs of puberty, her serum gonadotropin levels were suppressed (Table 2). The parents asserted that they had been compliant with the treatment regimen. Breast stage remained at III, and pubic hair advanced to stage IV by the end of therapy. As in patient 1, the diagnosis was revised to LHRH-independent precocious puberty. The family declined a trial of testolactone, and treatment was discontinued. Over the 2 yr after discontination of treatment, her bone age advanced, and her growth rate declined. By 2 yr, her gonadotropin response to LHRH had risen close to the pubertal range, and her predicted height was 152 cm.

Discussion

The persistent signs of puberty in these two girls contrast sharply with the more favorable responses of a previously reported group of children with LHRH-dependent precocious puberty who were treated with the same LHRH agonist (14). Although neither of the patients in this report had evidence of fibrous dysplasia of bone or café-au-lait pigment, we hypothesize that the mechanism of puberty in these patients is similar to the autonomous ovarian hyperfunction observed in MAS. Both of these patients presented with menstrual bleeding, as do a large proportion of patients with MAS, and both menstruated several times during LHRH agonist treatment. In addition, patient 2 developed unilateral ovarian cysts that waxed and waned over time, similar to the cysts observed in MAS (3, 15). Cysts were also detected in patient 1 during the fourth year of therapy, although their small size and ultrasonographic appearance were not unlike the those of ovarian cysts that may be seen in normal pubertal girls. Moreover, gonadotropin responses to LHRH had a prepubertal pattern before treatment, which can be expected early in the course of LHRH-independent precocious puberty (6) and remained prepubertal after LHRH agonist was discontinued. Thus, the clinical and hormonal features of the precocious puberty in these two patients are consistent with MAS. Since the extent of the skin and bone lesions in MAS is highly variable, we hypothesize that these two girls represent the circumstance in which the underlying defect of the MAS is expressed in the ovaries, but not in the skin or bones. Although not yet identified, this defect is thought to involve dysfunction of the signal systems that regulate cellular activity, which is expressed in only some cells of the affected organism as the result of a somatic mutation during embryonic development (16).

Our two subjects resemble previously reported patients with precocious puberty due to transient follicular cysts (17–20). However, unlike our two girls, most of these

patients had unsustained pubertal progression, and their clinical response to LHRH therapy was apparently not assessed. Nevertheless, the available data do not exclude the possibility of a similar underlying mechanism in many or all of these patients.

The decision to initiate LHRH agonist therapy and its continued use in these two girls deserve comment. First, at the time these patients started therapy, far less was known about the gonadotropin responses to LHRH agonists in children with LHRH-dependent precocious puberty and about the uniformity of treatment effectiveness. We also had yet to demonstrate the ineffectiveness of LHRH agonist in treating gonadotropin-independent precocious puberty due to MAS. Lastly, an additional factor is that some children with central precocious puberty who respond well to LHRH agonist presented initially with an apparently prepubertal pattern of gonadotropin response to LHRH (21). Such gonadotropin responses have also been seen in normal pubertal girls (12).

When the ineffectiveness of treatment in our two patients became apparent, initial efforts focussed on the possibility of noncompliance, although the suppression of gonadotropins suggested adequacy of therapy at the time of evaluation. Surprisingly, both sets of parents were convinced that therapy had improved the clinical picture in their children and resisted discontinuing it. Furthermore, effective alternative treatment for LHRH-independent puberty with an aromatase inhibitor was not established until late in the course of these girls' treatments. Although these factors prolonged the period of LHRH agonist treatment in these two children, we would now consider a 6- to 12-month therapeutic trial of LHRH agonist to be sufficient to confirm the response or lack of response in a child with early puberty whose diagnosis has not been established.

The optimal therapy for patients such as these two girls has still not been found. In patient 1, testolactone caused an initial response; however, during the second year, ovarian volume increased, and the patient menstruated. This suggested possible noncompliance, which the parents denied, or an escape from therapy, which has been seen in approximately half of our own group of MAS patients. We are currently evaluating the hypothesis that more potent inhibitors of aromatase will improve the response to treatment in these patients.

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